Median Nerve Shear Wave Elastography is Associated With the Neurophysiological Severity of Carpal Tunnel Syndrome

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Abbreviations

CSA, cross-sectional area; CTS, carpal tunnel syndrome; MN, median nerve; NCS, nerve conduction study; SWE, shear wave elastography; SWV, shear wave velocity; US, ultrasound; WFR, wrist-to-forearm ratio

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Objectives—This study examines the associations between the median nerve (MN) shear wave elastography (SWE), the MN cross-sectional area (CSA), patient's symptoms, and the neurophysiological severity of carpal tunnel syndrome (CTS). The most appropriate site to perform SWE was also tested.

Methods—This prospective study comprised 86 wrists of 47 consecutive patients who volunteered for MN ultrasound after an electrodiagnostic study. The neurophysiological severity of CTS was assessed according to the results of a nerve conduction study (NCS). The MN CSA was measured at the carpal tunnel inlet (wCSA) and the forearm (fCSA). SWE was performed on the MN in a longitudinal orientation at the wrist crease (wSWE), at the forearm (fSWE), and within the carpal tunnel (tSWE).

Results—The wCSA and wSWE correlated positively with the neurophysiological severity of CTS ($r = .619$, $P < .001$; $r = .582$, $P < .001$, respectively). The optimal cut-off values to discriminate the groups with normal NCS and with findings indicating CTS were 10.5 mm^2 for the wCSA and 4.12 m/s for the wSWE. With these cut-off values, wCSA had a sensitivity of 80% and specificity of 87% and wSWE a sensitivity of 88% and specificity of 76%. Neither tSWE nor fSWE correlated with the neurophysiological severity of CTS or differed between NCS negative and positive groups ($P = .429$, $P = .736$, respectively).

Conclusion—Shear wave velocity in the MN at the carpal tunnel inlet increases in CTS and correlates to the neurophysiological CTS severity equivalently to CSA measured at the same site.

Key Words—carpal tunnel syndrome; cross-sectional area; median nerve; shear wave elastography; ultrasound

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy in the human body.[1] The diagnosis of CTS is commonly based on symptoms, clinical findings, and nerve conduction studies (NCS). Ultrasound (US) can also be used as a complementary tool alongside NCS. Furthermore, in a recent expert consensus statement, it was agreed that the cross-sectional area (CSA) of the median nerve (MN) at the wrist is the most accurate parameter for assessing the status of the MN among the other widely studied US parameters.[2] However, the presented cut-off values for normal and abnormal CSA in previous literature vary, and thus far no consensus exists on a single optimal cut-off value.[2–4] Also, approximately 10–15% of patients with clinical CTS

have normal NCS.[5] According to a recent expert consensus, the best diagnostic accuracy is yielded when US and NCS are used in combination rather than either method alone, which increases the diagnostic yield by 13.5% on average.[2]

Shear wave elastography (SWE) is a rather new ultrasound-based method in which tissue stiffness is measured quantitatively. In SWE, bursts of focused US beams are transmitted to tissue to generate shear waves, and the propagation velocity of the waves generated is then measured. As shear waves propagate faster in dense and stiff tissues than in looser tissues, the elasticity properties of the tissue can be deduced from the velocity of the shear wave propagation. The stiffness is first measured as shear wave velocity (SWV) (m/s), but an elasticity parameter can also be calculated from the SWV. In most US devices the SWE algorithms assume homogenous and isotropic tissue, which potentially limits the applicability of SWE to study anisotropic nerve tissue.[6] However, it has recently been proposed that SWE has value in the diagnostics and follow-up of neuromuscular disorders, including peripheral entrapment neuropathies.[7–12] Furthermore, reports in the previous literature strongly indicate that MN stiffness is increased in CTS compared with healthy controls.[13–17] However, differences among scanning protocols of these studies and the variability of the used US devices limit the comparability of literature and the usability of the presented cut-off values in clinical practice.[11,12]

SWE might enhance the diagnosis of CTS by providing an additional viewpoint alongside NCS and traditional brightness mode (B-mode) US by evaluating the stiffness of the nerve alongside its functional capability and structure. The main aim of this basic research study was to examine how the MN stiffness compares to the NCS, the MN CSA and patient's symptoms in CTS. Another aim of this study was to determine whether a SWE measurement performed in the carpal tunnel inlet or within the carpal tunnel itself would be more accurate.

Materials and Methods

This prospective study comprised 86 wrists of 47 consecutive patients who volunteered for US after an electrodiagnostic study, which included NCS and needle-EMG. The patients had been referred to the Department of Clinical Neurophysiology due to variable symptoms in the upper extremities. Patients with findings of cervical radiculopathy, or findings suggesting polyneuropathy in the electrodiagnostic study were excluded. The Ethical committee of the local health care district approved the study, and all participants signed a written informed consent.

The included patients were asked whether they had experienced nocturnal symptoms of pain, numbness, or tingling in the sensory distribution of the MN (I–III digits and/or palmar surface), which are classically the first symptoms of CTS.[1] When such symptoms were reported, the duration of the symptoms was recorded in months. In addition, patients were asked about possible carpal tunnel surgical operation. If a wrist was reported as previously operated, it was not included to the study.

The electrodiagnostic study was performed before US by a clinical neurophysiologist or a resident in clinical neurophysiology. The neurophysiological severity of CTS was assessed based on the NCS results. The wrists were classified into four groups: normal, mild, moderate, and severe to extreme CTS.[18] In mild CTS, the MN sensory conduction velocity was more than 10 m/s slower than the sensory conduction velocity of the ulnar nerve. In moderate CTS, the motor distal latency of the MN was ≥4.2 ms in addition to the slowing of MN sensory conduction velocity in the same way as in mild CTS. In severe to extreme CTS, the sensory nerve action potentials were absent in addition to the prolonged MN motor distal latency. Furthermore, wrists classified as having normal NCS formed "the NCS negative group," and those wrists classified as having mild, moderate, and severe to extreme CTS formed "the NCS positive group." Needle-EMG was performed on the upper limb muscles from myotomes C5 to T1 to detect possible radiculopathy. In cases of bilateral symmetrical symptoms, only the more symptomatic upper limb was examined with needle-EMG. Patients with findings indicating radiculopathy or polyneuropathy were not included in the study.

The US examinations were all conducted by the same clinical neurophysiologist (KM), who had 4 years of experience with conventional B-mode imaging and 2 years with SWE and was blinded to the NCS results. The US device used was Samsung

RS85 Prestige with a linear transducer LA2-14A with an operating transmit frequency of 13 MHz. The study protocol was designed to follow the currently best-known recommendations for nerve SWE. It is recommended that nerves are studied in a longitudinal orientation, and the SWE results are reported in the form of SWV (m/s) because the elasticity parameter, which is reported in kilopascals (kPa), is computed from the SWV with an algorithm that assumes isotropic tissue and may somewhat vary between devices of different manufacturers.[5,11,12,19]

During US and SWE, the patients sat on a chair with their examined hand placed on a table in front of them. The patient's palm faced upwards with the fingers in a relaxed semiflexion. The angle of the patient's elbow was approximately 90° to avoid traction of the MN, which may falsely increase the SWV, and the patient was asked to relax during the examination. During SWE examination care was taken to not apply any extra pressure with the transducer.[14,15,20,21]

First, the MN was visualized in conventional B-mode imaging. The MN CSA was measured in transverse orientation to the nerve at two sites: at the wrist crease proximal to the carpal tunnel inlet where the MN was at its largest (wCSA) and the distal forearm (fCSA), approximately at the junction of the distal and middle thirds of the forearm. The CSA wrist-to-forearm ratio (CSA-WFR) was calculated by dividing the wCSA with the fCSA value.[22]

Next, the transducer was rotated 90° to obtain a longitudinal view of the MN. SWE was performed at three sites on the MN; at the wrist crease (wSWE), at the forearm (fSWE) at the site where the fCSA was measured, and at the carpal tunnel (tSWE). The wrist-to-forearm ratio for SWE (SWE-WFR) was also calculated by dividing the wSWE with the fSWE value.

In SWE, a 2D color stiffness map was applied to a B-mode image. The US device used also provided a reliable measurement index map in a dual image next to the SWE stiffness map. At each measurement site, the performer of the study selected three region of interest points inside the stiffness map on the MN so that the reliable measurement index of each point was close to maximum (1.0), and at least 0.6. The device manufacturer stated that 0.4 was the lowest acceptable value to achieve reliable SWV measurements. The mean of the three regions of interest points was recorded for each measurement site. The diameter of the region of interest was set to 3 mm. The B-mode US and SWE methods are demonstrated in Figures 1–3 for all measurement sites.

Statistical analyses were performed using the IBM SPSS Statistics 26 software. The correlations were tested with Spearman's rho. The statistical differences between groups were tested with ANOVA test, Mann–Whitney U test, or Kruskal–Wallis test, when appropriate. In multiple testing, the analyses were Bonferroni corrected.

Results

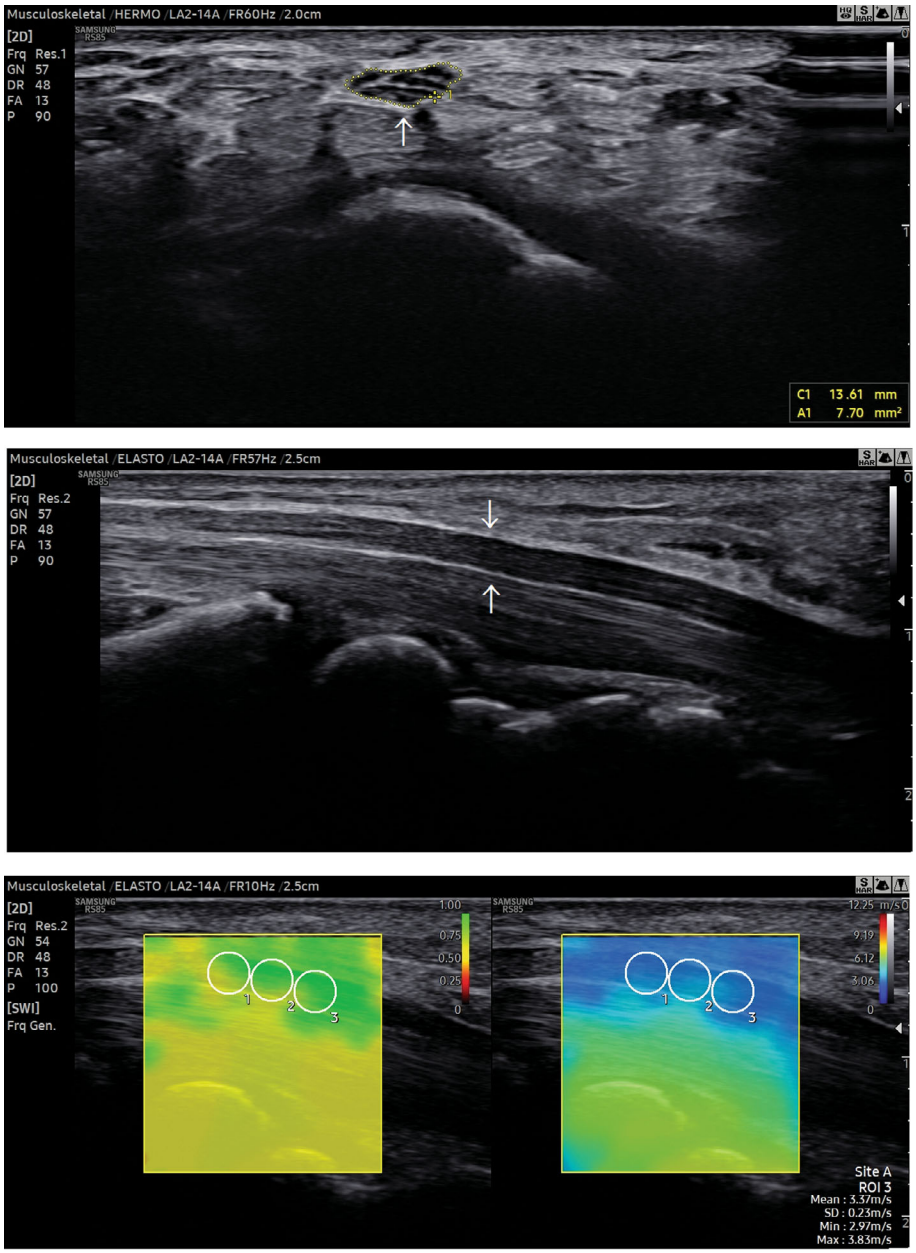
The study comprised 86 wrists of 47 patients. A total of 17 of the patients were male and 30 were female. Table 1 shows the descriptive values of the patients.

The wCSA was smaller in the NCS negative group than in the NCS positive group ($P < .001$). The wSWE was also lower in the NCS negative group than in the NCS positive group ($P < .001$). Both wCSA and wSWE correlated positively with the CTS severity groups ($r = .619$, $P < .001$; $r = .582$, $P < .001$, respectively). The descriptive values of the wCSA and the wSWE in different CTS severity groups are presented in Tables 2 and 3, respectively. The boxplots in Figures 4 and 5 demonstrate the differences in wCSA and wSWE between the severity groups. Figure 6 demonstrates a SWE stiffness map of a wrist with NCS findings of severe CTS. The CSA-WFR and SWE-WFR also correlated positively with the CTS severity groups ($r = .377$, $P < .001$; $r = .409$, $P < .001$, respectively).

The tSWE and fSWE showed no significant correlations with the severity groups. Furthermore, no difference was found in tSWE between the NCS negative and positive groups. wSWE did, however, correlate positively with tSWE in the NCS negative group ($r = .357$, $P = .005$), but not in the total study material or the NCS positive group.

A receiver operating characteristic (ROC) curve was calculated for both wCSA and wSWE (Figure 7) to differentiate between the NCS negative and the NCS positive groups. The area under the curve was 0.895 for wCSA (95% confidence interval 0.817–0.973) and 0.868 for wSWE (95% confidence interval 0.785–0.951). The cut-off values that equally optimize both sensitivity

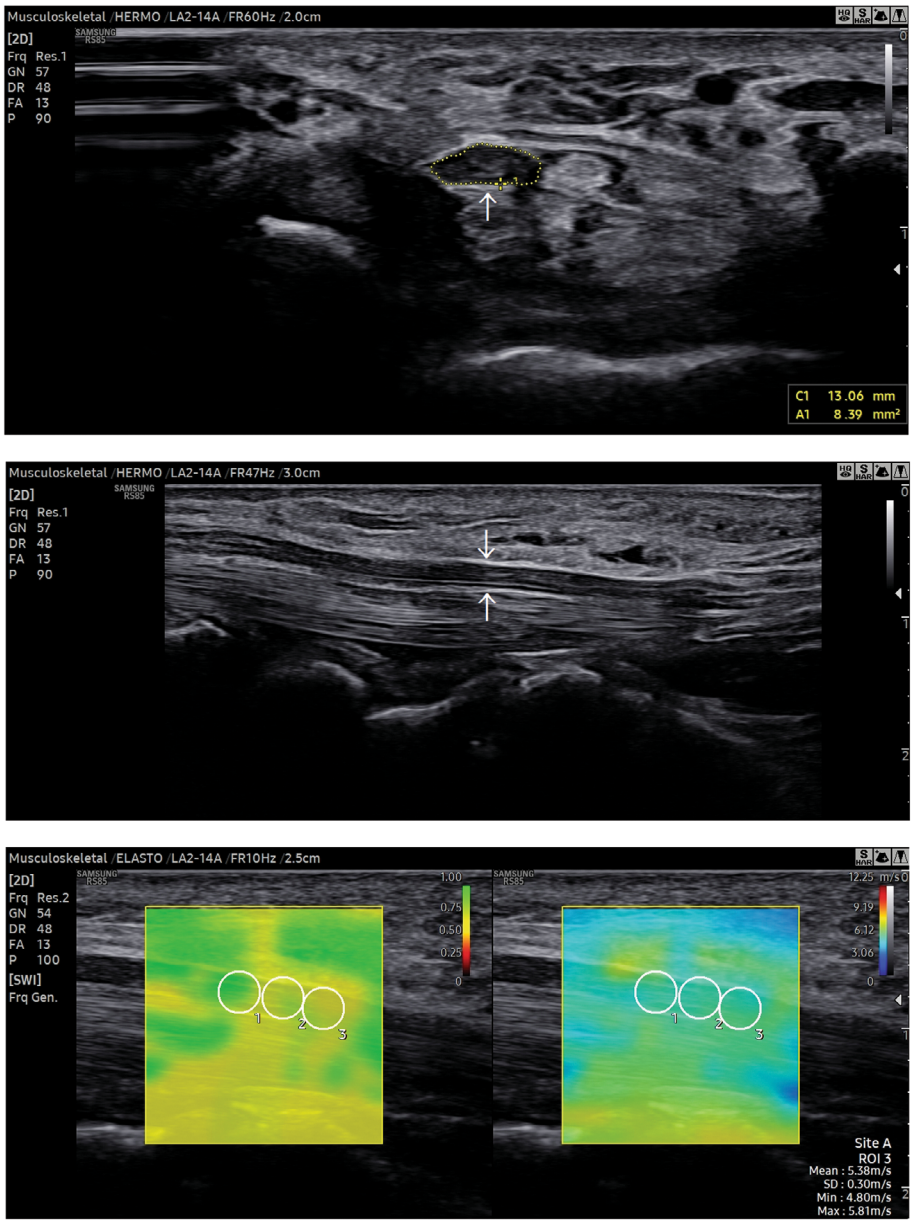
Figure 1. The median nerve (MN) at the carpal tunnel inlet, marked with arrows. The top image demonstrates the cross-sectional area measurement (wCSA) and the second image the longitudinal view of the MN in B-mode. The bottom image demonstrates the SWE method. MN is visualized in longitudinal orientation in a dual image. On the left, the overlaid color map shows the reliable measurement index. The SWE stiffness map is shown on the right. Three region of interest points are inserted on the MN. In the wrist shown, there were no signs of CTS in the NCS.



and specificity were 10.5 mm^2 for the wCSA and 4.12 m/s for the wSWE. With these limits, wCSA had a sensitivity of 80% and specificity of 87% and wSWE a sensitivity of 88% and specificity of 76%. Sensitivities and specificities of the other potential cut-off values are presented in Table 4.

Among the NCS negative group, wCSA correlated positively with patient BMI ($r = .288$, $P = .023$), but

Figure 2. The median nerve (MN) visualized within the carpal tunnel, marked with arrows. The top image demonstrates the transverse view of the MN and the second image the longitudinal view of the MN in B-mode. The bottom image demonstrates the SWE method. MN is visualized in longitudinal orientation in a dual image. On the left, the overlaid color map shows the reliable measurement index. The SWE stiffness map is shown on the right. Three region of interest points are inserted on the MN. In the wrist shown, there were no signs of CTS in the NCS.

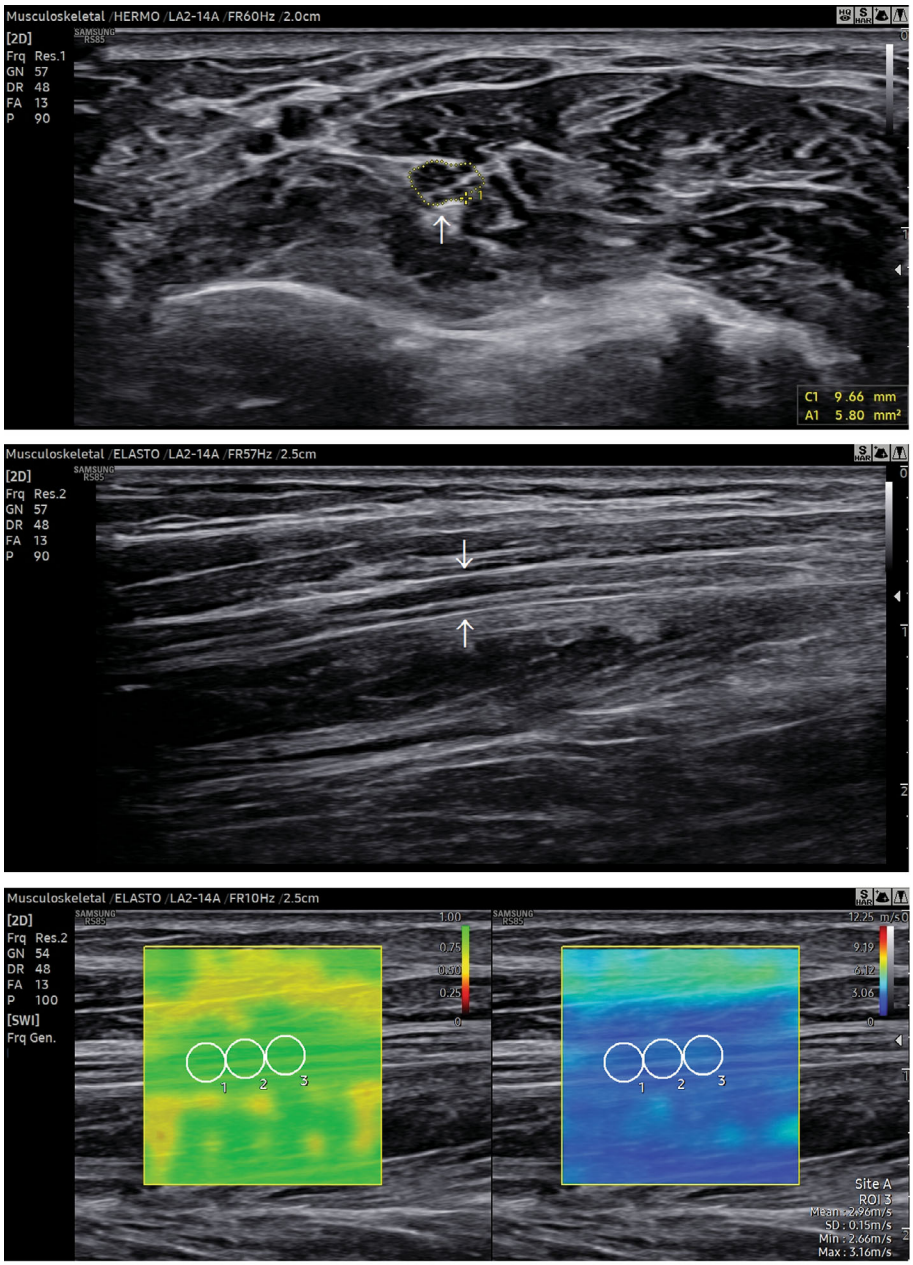


not with patient age, height, or weight. Furthermore, neither wSWE, fSWE, nor tSWE correlated with patient BMI, age, height, or weight.

In the NCS negative group, wSWE did not correlate with wCSA. However, in the total study material, wSWE correlated positively with wCSA ($r = .326$, $P = .001$). fSWE did not show statistically significant correlation with fCSA in the NCS negative group or in the total study material.

Both wCSA and wSWE were significantly higher among symptomatic patients compared with asymptomatic ($P = .002$ and $P = .009$, respectively). The mean

Figure 3. The median nerve (MN) at the forearm, marked with arrows. The top image demonstrates the site for cross-sectional area measurement at the forearm (fCSA) and the second image the longitudinal view of the MN in B-mode. The bottom image demonstrates the SWE method. MN is visualized in longitudinal orientation in a dual image. On the left, the overlaid color map shows the reliable measurement index. The SWE stiffness map is shown on the right. Three region of interest points are inserted on the MN. In the wrist shown, there were no signs of CTS in the NCS.



wCSA among patients without symptoms was 9.4 mm^2 (standard deviation $\pm$3.33 mm^2) and 12.1 mm^2 (standard deviation $\pm$4.59 mm^2) among patients reporting symptoms. The mean wSWE among patients without symptoms was 3.90 m/s (standard deviation $\pm$0.78 m/s) and 4.40 m/s (standard deviation $\pm$0.98 m/s) among patients reporting symptoms. The duration of symptoms did not show any significant correlation with wCSA or wSWE.

Table 1. The Descriptive Values of Patient Age, Height, Weight, and Body Mass Index (BMI)

	Minimum	Maximum	Mean	SD	Median
Age (years)	30	86	52	±16	52
Height (cm)	156	187	169	±8	169
Weight (kg)	50	128	77	±19	72
BMI	17.9	41.3	27.6	±5.9	26.9

SD, standard deviation.

Table 2. The Descriptive Values of the wCSA (mm^2) in Different Neurophysiological CTS Severity Groups

CTS Severity	Mean	SD	Median	Minimum	Maximum	% of Wrists
Normal	8.8	±1.8	9.0	4	13	72
Mild	12.0	±2.1	11.5	9	16	12
Moderate	14.2	±3.9	14.0	8	21	13
Severe to extreme	20.0	±11.0	20.0	9	31	3

SD, standard deviation.

Table 3. The Descriptive Values of the wSWE (m/s) in Different Neurophysiological CTS Severity Groups

CTS Severity	Mean	SD	Median	Minimum	Maximum	% of Wrists
Normal	3.73	±0.72	3.69	2.20	5.45	72
Mild	4.57	±0.60	4.60	3.28	5.38	12
Moderate	4.94	±0.68	5.15	3.82	5.72	13
Severe to extreme	5.11	±0.47	5.10	4.65	5.59	3

SD, standard deviation.

Figure 4. Boxplot showing the wCSA (mm^2) range (whiskers), median value (line in the box), and lower and upper quartile (box outline) in the CTS severity groups. The median CSA value was statistically different between the normal and mild and the normal and moderate groups. The Bonferroni corrected *P*-values of interest are shown in the figure.

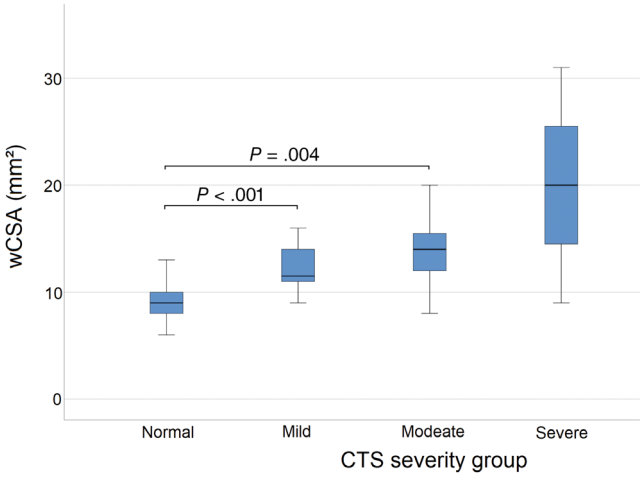


Figure 5. Boxplot showing the wSWE velocity (m/s) range (whiskers), median value (line in the box), and lower and upper quartile (box outline) in the CTS severity groups. The median value was statistically different between the normal and mild, normal and moderate, and normal and severe to extreme (named Severe in the figure) groups. The Bonferroni corrected *P*-values of interest are shown in the figure.

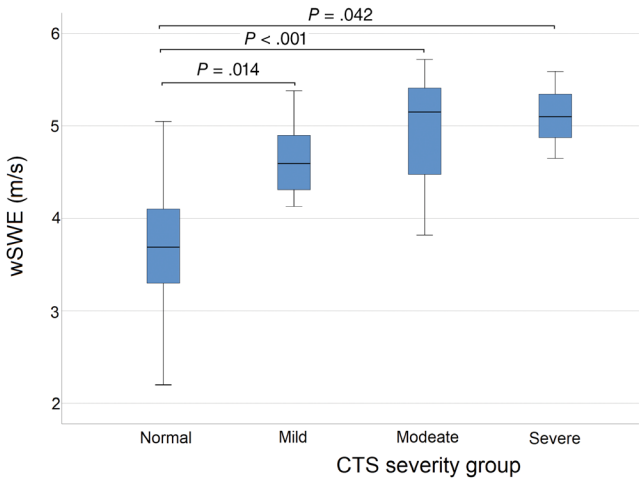


Figure 6. SWE-stiffness map at the carpal tunnel intel site in a wrist with severe CTS indicating nerve conduction study findings in a 57-year-old man. The cross-sectional area of the median nerve at the carpal tunnel inlet was 17 mm^2. The motor distal latency was prolonged to 7.4 ms.

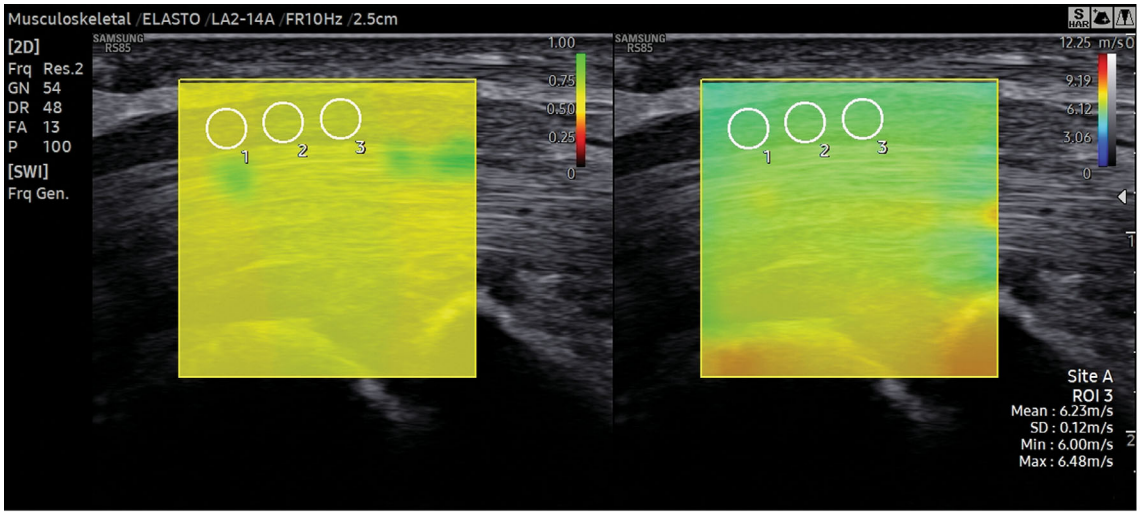
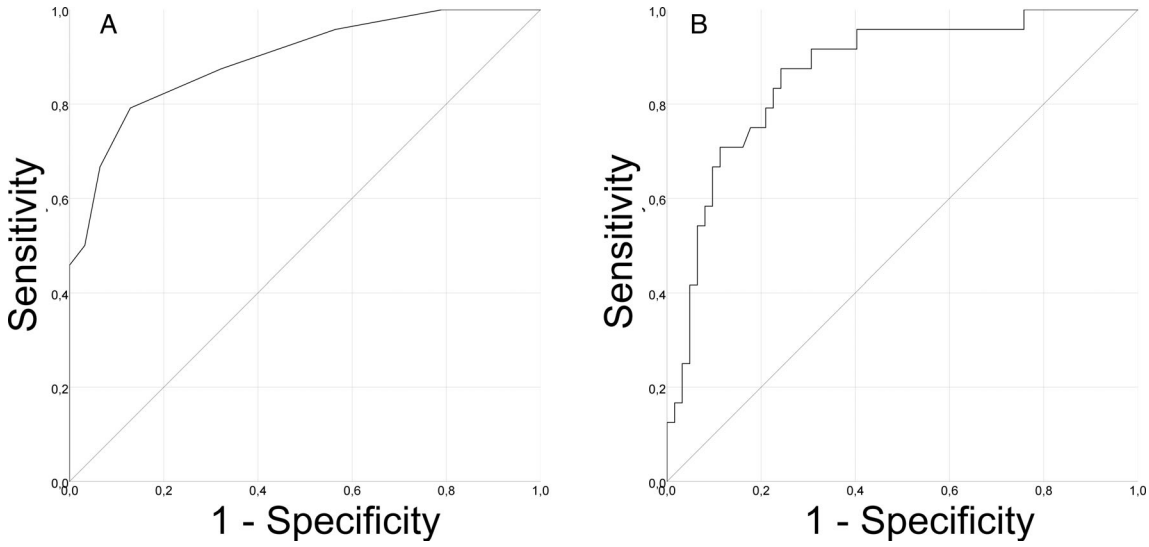


Figure 7. A, ROC curve of the wCSA and **B**, ROC curve of the wSWE to differentiate between the NCS-negative and NCS-positive groups.



Patients reported CTS-related symptoms in 16% of NCS-negative wrists and 75% of NCS-positive wrists (in 60% of wrists in the mild, 82% of wrists in the moderate, and 100% of wrists in the severe to extreme CTS category). Five symptomatic wrists that were in the NCS-positive group had wCSA ≤10 mm^2. Of these five wrists four had wSWE ≥4.12 m/s.

Discussion

The results of the present study show that SWE can bring additional value to the diagnostics of CTS. The wSWE correlated positively with the neurophysiological severity of CTS with an almost equal correlation coefficient as the traditionally used wCSA. According

Table 4. Sensitivity and 1-Specificity for the Different Cut-Off Values of the wCSA and the wSWE

wCSA			wSWE		
Value (mm^2)	Sensitivity	1-Specificity	Value (m/s)	Sensitivity	1-Specificity
7.5	1.000	0.790	3.26	1.000	0.758
8.5	0.958	0.565	3.88	0.917	0.355
9.5	0.875	0.323	4.06	0.875	0.274
10.5	0.792	0.129	4.12	0.875	0.242
11.5	0.667	0.065	4.61	0.667	0.097
12.5	0.500	0.032	5.03	0.417	0.065
13.5	0.458	0.000	5.52	0.125	0.000

to the ROC analysis, SWE is also comparable to wCSA in its capability to diagnose CTS. Although the specificity of wCSA (87%) is slightly higher than the specificity of wSWE (76%), the sensitivity of wSWE (88%) is slightly higher than the sensitivity of wCSA (80%). This is when the NCS is used as a gold standard. Moreover, according to the correlation coefficients, it also seems that the SWE-based wrist-to-forearm ratio is associated with the neurophysiological severity of CTS in a similar manner as the CSA-based WFR.

The results of this study also verify that it is better to perform SWE at the carpal tunnel inlet than within the carpal tunnel, as tSWE did not correlate with CTS severity. Among healthy wrists, tSWE correlated mildly positively with wSWE. However, the parameters did not correlate in wrists with CTS. This could be explained by the intra-tunnel pressure inside the carpal tunnel, which may vary in CTS.[17,23] Also, the anatomy of the carpal tunnel, which is a tight compartment with stiff layers of fascia and tendons surrounding the MN, may impair the capability of SWE to perform inside the carpal tunnel. fSWE did not correlate to the neurophysiological CTS severity, which may be explained simply by a too long distance to the compression site.

As stated in the introduction, the nerve SWE protocols used in the previous literature vary extensively, which is understandable since SWE is not yet an established method in diagnostics of peripheral neuropathies. To our knowledge, one study to date has investigated the stiffness of the MN in CTS using a study protocol similar to ours (longitudinal orientation and using the SWV [m/s] instead of the elasticity parameter [kPa]).[24] Zhang et al combined patients with mild and moderate CTS in one group (group A) and patients with severe to extreme CTS in another (group B). In their study, the mean SWV in group A was 3.248 ± 0.410 m/s and 5.241 ± 0.545 m/s in group B. The mean SWV in a control group was 2.542 ± 0.368 m/s. Their results are comparable to ours, even though the absolute SWV values are slightly slower. However, Zhang et al used a different US device, which might explain the slight difference in the absolute values.

As a rather new application, many of the effects of patient characteristics on the nerve SWE results are still unknown. Moreover, it has been questioned whether the size of the nerve affects the SWV.[11] In our study, the wCSA and the wSWE did not correlate in the NCS negative group, and neither did the fCSA and the fSWE. There was a positive correlation between wCSA and wSWE in the total study material. However, this may have been because wSWE is positively correlated with the neurophysiological CTS severity, where the MN CSA is increased. Thus, it seems that the size of the MN does not affect the SWV in healthy wrists.

The wSWE was not associated with patient age, height, weight, or BMI. However, the wCSA was positively associated with patient BMI, which has also been reported in the previous literature.[25–27] The correlation is rather mild and should be studied in a larger population to verify the clinical applicability. However, it can be speculated that SWE could bring additional information in cases where it is unclear whether the CSA enlargement is associated with CTS or obesity.

As presented in the Introduction, the diagnostics of CTS include considerations of clinical aspects and should not be solely based on the NCS. In the NCS-negative group, patients reported CTS-related

symptoms in 16% of wrists. Considering that approximately 10–15% of patients with clinical CTS have normal NCS,[5] it can be that some symptomatic patients could truly have had CTS even though the NCS failed to point it out. Therefore, it is possible that some patients in the NCS negative group had CTS and subsequently showed correctly high wCSA and/or wSWE. These wrists would have been interpreted as false positives in the ROC analysis. Therefore, patient symptoms should also be addressed in future studies that aim to assess the clinical diagnostic accuracy of SWE in CTS. Although, it must also be noted that the most sensitive tests for CTS in the NCS, such as measurement of the palm-wrist segment or a short segment study, were not performed, and very mild cases of CTS may have therefore been classified into the NCS negative group.

This study has limitations that need to be addressed, perhaps most important of which is the small sample size. However, our results are consistent with those in the previous literature. Second, the CSA and SWE measurements were performed by the same physician who was not blinded to the US results while conducting the SWE. Both parameters are, however, objective, and the measurement sites were agreed beforehand, thus reducing the possibility of bias. Third, the CSA was measured only from the inlet of the carpal tunnel. However, in some cases the enlargement of the nerve can be found distal to the carpal tunnel.[2] Thus, the association between the enlarged CSA and the neurophysiological CTS severity could have been even stronger if the entire area of the carpal tunnel and its proximity was scanned and the CSA was measured at the site where it was at its largest. However, the study did not aim to test the accuracy of the wCSA in the diagnostics for CTS, but to test the capability of SWE to perform in CTS by comparing the SWE results to wCSA and NCS. Also, the capability of SWE to perform at the palmar area and thus relevance of the measurement can be questioned, as the site consists of a mix of different tissue types of varying elasticity properties overlying the MN. Finally, even though SWE can be used in diagnostics of CTS, caution must be taken when it is used in anisotropic tissues such as nerves. As already mentioned, the application, including the reliable measurement index algorithm, is designed for isotropic tissues, which may reduce its adequacy in anisotropic tissues. The reliable measurement index was used in this study to guide the placement of the region of interest points.

In conclusion, this study shows that the MN SWV measured at the carpal tunnel inlet is associated with the neurophysiological severity of CTS similarly to the MN CSA at the wrist. Also, a WFR based on SWV measurements can be calculated and used in CTS assessment. The results of the present study also reveal that SWV does not seem to be dependent on MN size. Thus, SWE is a new potential method in diagnostics of CTS. It brings forth another point of view to the assessment of the status of the MN, alongside with assessing the structure of the MN with the conventional US B-mode imaging and with assessing the MN function with the NCS. However, it is left for future research to study in which cases addition of SWE to the NCS and CSA measurement can enhance the clinical diagnostic accuracy of CTS. According to this study, patients with obesity could benefit from SWE.

In the future, a generally recognized nerve SWE scanning protocol is needed for uniformity and enhanced comparability in the literature. Also differences in SWE applications between different US device manufacturers limit the utility of reported SWV values. The US device manufacturers are also encouraged to recognize the possibilities of SWE in anisotropic tissues in future development of the application.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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